REMARKS

Status of the Claims

By this amendment, claims 8, 12, 14, and 15 are amended and claims 16 and 17 are added. Upon entry of this Amendment, claims 8-17 will be pending in the application.

Exemplary support for the amendments to claim 8 is found in Examples 2 and 3. Exemplary support for the amendments to claim 14 is found in Examples 2, 3 and 5. Exemplary support for newly added claims 16 and 17 is found in originally filed claim 15, as well as in Examples 2, 3 and 5.

Claim Rejections - 35 U.S.C. § 112, Second Paragraph

Claims 8-15 are rejected by the Examiner under 35 U.S.C. § 112, second paragraph, as being indefinite. Applicants respectfully request reconsideration and withdrawal of the rejections.

A) The Examiner asserts that in claims 8-13 it is unclear as to what Formula I encompasses. Applicants have amended claims 8 and 12 to recite the actual formula of Formula I, as suggested by the Examiner.

B) The Examiner asserts that in step (a) of claim 8, the phrase "one or more indolinone compounds" is unclear. Applicants have amended step (a) of claim 8 to recite "one or more indolinone compounds of Formula I", as suggested by the Examiner.

C) The Examiner asserts that in claims 8-13, it is not clear what "effect" is being monitored. Applicants respectfully disagree with the Examiner's assertion and direct the Examiner's attention to page 27, lines 11-15 where the term "therapeutic effect" is defined. A person of ordinary skill in the art reading the specification would know that an "effect" refers to the result an agent has on cell growth or other factors causing or contributing to an abnormal condition. Additionally, Examples 2 and 3 describe measuring the effect of

indolinone compounds on various cells. For example, in Example 3 an effect that was measured was the inhibition of a growth factor stimulated proliferation of smooth muscle cells. Applicants have amended part (c) of claim 8 to recite "monitoring an inhibitory effect on growth factor stimulated cell proliferation".

D) The Examiner asserts that in claims 12 and 13, the phrase "general disease symptoms" is unclear because the possible symptoms recited in the specification do not provide a clear definition of what is encompassed by the term "general disease symptoms". Applicants respectfully disagree with the Examiner's assertion and direct the Examiner's attention to pages 27-28 and page 36, line 19 through page 51, line 22 where detailed descriptions of various disease states are provided. A person of ordinary skill in the art would know what is encompassed by the term "general disease symptoms" from the description provided in the specification and their own knowledge of the particular disease. For example, the specification describes "rheumatoid arthritis" on page 27, lines 16-20 as being "marked by synovial membranes and articular structures and by muscle atrophy and rarefaction of the bones." From this description, as well as based on one's own knowledge, a person of ordinary skill in the art would know the symptoms that a patient with rheumatoid arthritis would present. Ear nodulation, tail nodulation, nose swelling, paw swelling and ballanitis are indicative of a specific disease state and are used for testing purposes of the same.

E) The Examiner asserts that in claims 12 and 13, the term "active" is unclear. Applicants respectfully disagree with the Examiner's assertion and direct the Examiner's attention to Example 4 of the specification which clearly describes calculation of the arthritis index and references tables 6 and 7 for a summary of effects on disease symptoms. A person of ordinary skill in the art would know that the arthritis index calculated for animals that were administered a test substance would be indicative of the activity of the test substance.

F) The Examiner asserts that in claim 14, it is not clear whether the method is a method for modulating the activity of VEGF, FGF, or PDGF on cells *in vivo* or *in vitro or* in modulating tyrosine kinase signal transduction. Applicants have amended claim 14 to be directed to a method of inhibiting VEGF, FGF, or PDGF stimulated cell proliferation in vein endothelial cells or smooth muscle cells. Applicants have also added claim 16 (directed to a

method of A method of inhibiting VEGF, FGF, or PDGF stimulated cell proliferation in vein endothelial cells or smooth muscle cells *in vivo*) and claim 17 (directed to a method of A method of inhibiting VEGF, FGF, or PDGF stimulated cell proliferation in vein endothelial cells or smooth muscle cells *in vitro*).

G) The Examiner asserts that in claim 14, the term "*in vitro*" is indefinite because it is unclear how this is an *in vitro* method because the first step of the method involves administering to a patient in need. Applicants have amended claim 14 to be directed a method of inhibiting VEGF, FGF, or PDGF stimulated cell proliferation in vein endothelial cells or smooth muscle cells. Claim 17 is directed a method of inhibiting VEGF, FGF, or PDGF stimulated cell proliferation in vein endothelial cells or smooth muscle cells *in vitro* and does not involve administering to a patient in need. Support for newly added claim 18 is found in the specification on page 51, line 24, through page 52, line 27.

H) The Examiner asserts that in claims 14 and 15, the recitation "said one or more compounds of formula I" lacks antecedent basis. Applicants have amended claims 14 and 15 by deleting the term "said".

I) The Examiner asserts that in claim 14, the phrase "one or more pharmaceutically acceptable recipients" is indefinite because the claim does not refer to a first pharmaceutically acceptable recipient, only a "pharmaceutically acceptable composition". Applicants note that claim 14 refers to "one or more pharmaceutically acceptable excipients". Therefore, claims 14 and 15 comply with the requirements of 35 U.S.C. § 112, second paragraph.

J) The Examiner asserts that in claims 14 and 15, it is unclear whether "and a five-membered ring" should be considered "open" or "closed" claim language. Applicants have amended claims 14 and 15 by deleting the phrase "and a five-membered heteroaryl ring, wherein said five-membered ring is selected from the group consisting of".

K) The Examiner asserts that in claim 15 the phrase "solid tumor growth and metastases" is unclear. Applicants respectfully disagree with the Examiner's assertion and

direct the Examiner's attention to the specification at page 28, lines 2-4 and page 37, line 4, through page 41, line 20 where these terms are clearly described.

L) The Examiner asserts that in claim 15 the phrase "excessive scarring during wound healing" is unclear. Applicants respectfully disagree with the Examiner's assertion and direct the Examiner's attention to page 28, lines 18-21 where a definition of this term is recited.

Claim Rejections - 35 U.S.C. § 112, First Paragraph

Claims 14 and 15 were rejected by the Examiner under 35 U.S.C. § 112, first paragraph, for lack of written description and lack of enablement. Applicants respectfully request reconsideration and withdrawal of the rejections.

A. Claim 14

The Examiner asserts that the claimed method encompasses an extremely vast genus of possible genes that could be activated or deactivated, as well as possible proteins that have an altered expression. Applicants have amended the claims to be directed to a method of inhibiting VEGF, FGF, or PDGF stimulated cell proliferation in vein endothelial cells or smooth muscle cells. Both written description and enablement are provided in the specification. See, for example, Examples 2, 3 and 5. While the Examples are directed to human vein endothelial cells and rat smooth muscle cells, it is not necessary to amend the claims to recite cells from these specific organisms, as human and rat cells are model cells representative of cells from any organism.

B. Claim 15

The Examiner asserts that the specification only provides sufficient written description and enablement for a method of treating and/or preventing arthritis. Applicants respectfully disagree.

Claim 15 is directed to a method treating and/or preventing an abnormal condition selected from the group consisting of arthritis, endometriosis, ocular neovascularization, solid

tumor growth and metastases, and excessive scarring during wound healing. These abnormal conditions are blood vessel proliferative disorders, referred to as angiogenesis and/or vasculogenesis, which result from abnormal cell proliferation. For example, on page 2, lines 19-21 of the specification, it states that arthritis and endometriosis are dominated by abnormal neovascularization and/or unregulated angiogenesis. On page 44, lines 12-26 of the specification, the relationship of ocular neovascularization and angiogenesis is disclosed. On page 37, line 5 through page 38, line 5 of the specification, the link between angiogenesis and tumor growth/metastasis is described. Additionally, on page 28, lines 18-21 of the specification, the relationship of angiogenesis and neovascularization to excessive scarring during wound healing is described.

A person of ordinary skill in the art would not endure undue experimentation in order to treat or prevent the abnormal conditions of claim 15 because all of these diseases are characterized by abnormal neovascularization and/or unregulated angiogenesis. The disclosure in the specification of treatment of arthritis is an example of treating a disease characterized by abnormal neovascularization and/or unregulated angiogenesis with the presently claimed method. Additionally, Applicants are not limited to their enumerated examples. Therefore, a person of ordinary skill in the art could apply the teachings from the specification to treatment or prevention of endometriosis, ocular neovascularization, solid tumor growth and metastases, and excessive scarring during wound healing without undue experimentation.

Claim Rejections - Double Patenting

Claims 14 and 15 were rejected by the Examiner under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 15-21 of U.S. Patent No. 5,792,783. Attached herewith is a terminal disclaimer which disclaims the terminal part of the term of any patent granted on the above-identified application which would extend beyond the full statutory term, as presently shortened by any terminal disclaimer, of U.S. Patent No. 5,792,783. Therefore, the rejection is moot.

CONCLUSION

As the above-presented amendments and remarks address and overcome all of the rejections presented by the examiner, withdrawal of the rejections and allowance of the claims are respectfully requested.

If the examiner has any questions concerning this application, he or she is requested to contact the undersigned.

Respectfully submitted,

Date March 19 2003

By #46,785

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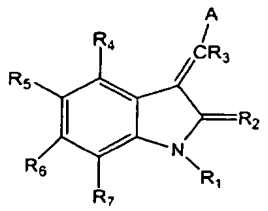
Should additional fees be necessary in connection with the filing of this paper, or if a petition for extension of time is required for timely acceptance of same, the Commissioner is hereby authorized to charge Deposit Account No. 19-0741 for any such fees; and applicant(s) hereby petition for any needed extension of time.

VERSION WITH MARKINGS TO SHOW CHANGES MADE

8. (Amended) A method of identifying one or more indolinone compounds of Formula I

(I) 

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that inhibit growth factor-stimulated cell proliferation comprising the following steps:

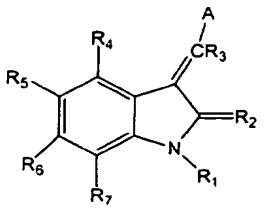
(a) contacting cells with one or more indolinone compounds;

(b) contacting said cells with one or more growth factors selected from the group consisting of VEGF, PDGF, and FGF;

(c) monitoring an inhibitory effect on growth factor stimulated cell proliferation; [effect upon said cells;] and

(d) identifying indolinone compounds of formula I that inhibit growth factor-stimulated cell proliferation.

12. (Amended) A method of identifying one or more indolinone compounds of Formula I

(I) 

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that are active in an adjuvant arthritis model in rats comprising the following steps:

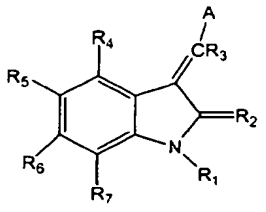
(a) administering said one or more indolinone compounds to said rats;

(b) monitoring an effect upon general disease symptoms in said rats; and

(c) identifying indolinone compounds of formula I that are active in an adjuvant arthritis model in rats.

14. (2X Amended) A method of [modulating abnormal cell proliferation, modulating the activity of] inhibiting VEGF, FGF, or PDGF stimulated cell proliferation in vein endothelial cells or smooth muscle cells [on cells *in vivo* or *in vitro* or modulating tyrosine kinase signal transduction,] comprising administering to a patient in need of such treatment a [pharmaceutically acceptable] composition comprising a therapeutically effective amount of [said] one or more compounds of formula I,

wherein said composition optionally includes one more pharmaceutically acceptable excipients in at least one of parenteral, oral, or topical formulation:

(I) 

wherein,

R_1 is H or alkyl;

R_2 is O or S;

R_3 is H;

R_4, R_5, R_6, and R_7 are each independently selected from the group consisting of hydrogen alkyl, alkoxy, aryl, aryloxy, alkaryl, alkaryloxy, halogen, trihalomethyl, S(O)R, SO_2NRR', SO_3R, SR, NO_2, NRR', OH, CN, C(O)R, OC(O)R, NHC(O)R, $(CH_2)_nCO_2R$, CONRR', and $(CH_2)_nONRR'$;

A is selected from the group consisting of [a] 4,5,6,7-tetrahydroindole, [and a five-membered heteroaryl ring, wherein said five-membered ring is selected from the group consisting of] thiophene, pyrrole, pyrazole, imidazole, 1,2,3-triazole, 1,2,4-triazole, oxazole, isoxazole, thiazole, isothiazole, 2-sulfonylfuran, 4-alkylfuran, 1,2,3-oxadiazole, 1,2,4-oxadiazole, 1,2,5-oxadiazole, 1,3,4-oxadiazole, 1,2,3,4,-oxatriazole, 1,2,3,5-oxatriazole, 1,2,3-thiadiazole, 1,2,4-thiadiazole, 1,2,5-thiadiazole, 1,3,4-thiadaizole, 1,2,3,4-thiatriazole, 1,2,3,5-thiatriazole, and tetrazole, wherein said [five-membered ring and said tetrahydroindole are] group is optionally substituted with one or more substituents selected from the group consisting of alkyl, alkoxy, aryl, aryloxy, alkaryl, alkaryloxy, halogen, trihalomethyl, S(O)R, SO_2NRR', SO_3R, SR, NO_2, NRR', OH, CN, C(O)R, OC(O)R, NHC(O)R, $(CH_2)_nCO_2R$, CONRR', and $(CH_2)_nONRR'$;

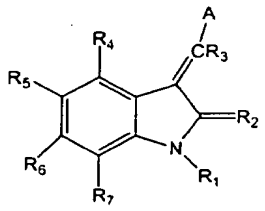
n is 0-3;

R is selected from the group consisting of H, alkyl, and aryl; and

R' is selected from the group consisting of H, alkyl, and aryl, wherein said alkyl is optionally substituted with a six-membered heteroaliphatic ring, and wherein said six-membered ring is optionally substituted at one or more positions with substituents selected from the group consisting of alkyl, alkoxy, halogen, trihalomethyl, NO_2, and $(CH_2)_nCO_2R$.

15. (2X Amended) A method of treating or preventing an abnormal condition by administering to a patient in need of such treatment a pharmaceutically acceptable composition comprising a therapeutically effective amount of [said] one or more compounds of formula I,

wherein said abnormal condition is selected from the group consisting of arthritis, endometriosis, ocular neovascularization, solid tumor growth and metastases, and excessive scarring during wound healing, wherein said composition optionally includes one or more pharmaceutically acceptable excipients in at least one of parenteral, oral, or topical formulation:

(I) 

wherein,

R_1 is H or alkyl;

R_2 is O or S;

R_3 is H;

R_4, R_5, R_6, and R_7 are each independently selected from the group consisting of hydrogen alkyl, alkoxy, aryl, aryloxy, alkaryl, alkaryloxy, halogen, trihalomethyl, S(O)R, SO_2NRR', SO_3R, SR, NO_2, NRR', OH, CN, C(O)R, OC(O)R, NHC(O)R, $(CH_2)_nCO_2R$, CONRR', and $(CH_2)_nONRR'$;

A is selected from the group consisting of [a] 4,5,6,7-tetrahydroindole, [and a five-membered heteroaryl ring, wherein said five-membered ring is selected from the group consisting of] thiophene, pyrrole, pyrazole, imidazole, 1,2,3-triazole, 1,2,4-triazole, oxazole,

isoxazole, thiazole, isothiazole, 2-sulfonylfuran, 4-alkylfuran, 1,2,3-oxadiazole, 1,2,4-oxadiazole, 1,2,5-oxadiazole, 1,3,4-oxadiazole, 1,2,3,4,-oxatriazole, 1,2,3,5-oxatriazole, 1,2,3-thiadiazole, 1,2,4-thiadiazole, 1,2,5-thiadiazole, 1,3,4-thiadaizole, 1,2,3,4-thiatriazole, 1,2,3,5-thiatriazole, and tetrazole, wherein said [five-membered ring and said tetrahydroindole are] group is optionally substituted with one or more substituents selected from the group consisting of alkyl, alkoxy, aryl, aryloxy, alkaryl, alkaryloxy, halogen, trihalomethyl, S(O)R, SO_2NRR', SO_3R, SR, NO_2, NRR', OH, CN, C(O)R, OC(O)R, NHC(O)R, $(CH_2)_nCO_2R$, CONRR', and $(CH_2)_nONRR'$;

n is 0-3;

R is selected from the group consisting of H, alkyl, and aryl; and

R' is selected from the group consisting of H, alkyl, and aryl, wherein said alkyl is optionally substituted with a six-membered heteroaliphatic ring, and wherein said six-membered ring is optionally substituted at one or more positions with substituents selected from the group consisting of alkyl, alkoxy, halogen, trihalomethyl, NO_2, and $(CH_2)_nCO_2R$.